The Clot Thickens: The mysteries of coagulopathies revealed

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Learning Objectives

1. Describe the physiology of the coagulation process.

2. Understand the complexities of coagulopathies in the context of the critically ill patient.

3. Discuss the etiology, pathophysiology, clinical manifestations and treatment of coagulopathies pertinent to the critically ill patient.
Outline

1. Introduction – concept mapping
2. Review normal hemostasis
3. Disseminated intravascular coagulation
4. Venous thromboembolism (Pulmonary embolus and deep vein thrombosis) & anti-phospholipid syndrome
5. Heparin induced thrombocytopenia
6. Putting it together – Case studies
Introduction – Concept Mapping
Normal Hemostasis

Four physical events:
- Vascular constriction
- Platelet plugging
- Blood clot formation
- Fibrinolysis
Vascular Constriction

- Occurs within seconds, lasts minutes to hours
- Reduces blood flow – blood loss
- Degree of contraction is directly related to extent of injury

Platelet Plugging

- Platelets become ‘sticky’
- Activation of platelet - release of mediators
  - Attract more platelets
  - Thromboxane A2 - procoagulant
- Develops within 3-5 min

Blood Clot Formation

- Tissue factor and factor VII initiate clotting cascade
- Conversion of prothrombin to thrombin

**Thrombin**
- Stimulates platelets
- Amplifies clotting cascade
- Cleaves fibrinogen to fibrin

- Develops within 3-5 min

Fibrinolysis

- Dissolution of clot
- Conversion of plasminogen to plasmin
- Plasmin
  - Digestion of fibrinogen and fibrin
  - Fibrin degradation products (FDPs)
  - Inactivation of clotting factors V and VIII

(Huether, Rote, & McCance, 2019, p 916)
Summary: Normal Hemostasis

Four physical events:

- Vascular constriction: immediate local reaction
- Platelet plugging: immediate, platelets become sticky, thromboxane A2 mediated
- Blood clot formation: prothrombin converted to thrombin, amplification of clotting cascade
- Fibrinolysis: plasminogen converted to plasmin, breaks down clot, FDPs
Disseminated Intravascular Coagulation

- Consumptive coagulopathy
- Secondary complication
- Microcirculation clotting and bleeding
- Mortality rate for acute DIC 50-80%
### Clinical Condition Associated with DIC

- Sepsis/septic shock
- Malignancy
- Obstetrics
- Intravascular hemolysis
- Vascular disorders
- Liver disease
- Intravascular prosthetic devices
- Acidosis and alkalosis
- Trauma & burns
- Cardiovascular diseases
- Toxins
Pathophysiology of DIC

- Trigger creates procoagulant environment
  - Tumour necrosis factor – extrinsic pathway stimulation
  - Endotoxins – inhibit protein C (anticoagulant)
  - Intrinsic pathway stimulation – endothelial damage

- Increase in procoagulants
  - Prothrombin
  - Factor V
  - Factor VII
  - Platelets
Pathophysiology of DIC

- Fibrinolytic system stimulation
  - Lysis of microclots
  - Production of FDPs (anticoagulant)
Clinical Manifestations

- Systemic problem therefore symptoms related to clotting or bleeding and can effect any system
- Bleeding is the predominant coagulopathy
  - Oozing from catheters, drains and sites of trauma
- End organ dysfunction related to ischemia
## Clinical Manifestations - Bleeding

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Manifestation - bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>• Hematuria</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>• Hemoptysis</td>
</tr>
<tr>
<td>Neurological</td>
<td>• Decreased LOC</td>
</tr>
<tr>
<td></td>
<td>• Delirium</td>
</tr>
<tr>
<td></td>
<td>• Transient focal neurological symptoms</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td>• Vomiting (hematemesis)</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea (hematochezia, melena stools)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Bruising</td>
</tr>
<tr>
<td></td>
<td>• Bleeding</td>
</tr>
<tr>
<td></td>
<td>• Petechiae</td>
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</tbody>
</table>
Clinical Manifestations - Clotting

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Manifestation - clotting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>• Proteinuria</td>
</tr>
<tr>
<td></td>
<td>• Acute oliguria</td>
</tr>
<tr>
<td></td>
<td>• Anuria</td>
</tr>
<tr>
<td>Hepatic</td>
<td>• Jaundice</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>• Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>• Acidosis</td>
</tr>
<tr>
<td></td>
<td>• Dyspnea</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Decreased tissue perfusion</td>
</tr>
<tr>
<td></td>
<td>• Necrosis</td>
</tr>
</tbody>
</table>
Laboratory Findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Reduced</td>
</tr>
<tr>
<td>Prothrombin time/ international normalized ratio (PT/INR)</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>Reduced</td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>Elevated</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Treatment

1. High level of suspicion and monitoring for DIC
2. Identify and eliminate underlying cause (trigger)
3. Address the coagulant state of the patient
   a) Stop the microvascular clotting
   b) Replace coagulant constituents
4. Supportive care
Summary DIC

- Systemic, consumptive, secondary disorder
- Initially procoagulant, shifts to anticoagulant
- Primarily present with widespread bleeding
- Labs show decreased platelets and fibrinogen and increased PT/INR, PTT, FDP and D-dimer
- Treatment: Prevent, remove underlying cause, supportive care and blood products
Procoagulation State

VENOUS THROMBOEMBOLIC (VTE)

- DEEP VEIN THROMBOSIS (DVT)
- PULMONARY EMBOLUS (PE)
Normal Innate Prevention of Thrombosis

1. Thrombomodulin (present on surface of cell) activates clotting factors, converts fibrinogen into fibrin.

2. THROMBIN binds to Thrombomodulin.

Tissue factor pathway inhibitor (TFPI) (produced by E cells/platelets)

Anti thrombin III (AT III) (Binds to endogenous Heparin)

Endothelial Cell or Platelet

Protein S

Protein C
Risk Factors

Inherited disorders

**Immobility**

Reproductive: Pregnancy, oral contraceptives

Malignancy

Trauma/surgery
Virchow's Triad

- Venous Stasis
- Vessel injury
- Hypercoagulable State
  - Primary
  - Secondary
Prevention of VTE: Things to Consider

- Know the risk factors – who should you be monitoring for VTE?
- SCD’s, Anticoagulant therapy, Fluids, Ambulation
Deep Vein Thrombosis

- Virchow’s Triad
- Clot formation
- Vein destruction
- Emboli
Pulmonary Embolism

- Virchow’s Triad
- Deep Vein Thrombosis (DVT)
- Migration
Pathogenesis, Mechanism, Manifestations of PE

**Decreased pulmonary blood flow**
- CO2/O2 exchange poor
  - CO2 buildup sensed by medullary chemo receptors to increase RR
  - Dyspnea / Shortness of breath
- Low O2 detected by aortic/carotid chemoreceptors signals brain to increase RR and HR

**Pulmonary Artery Obstruction**
- Good ventilation, not good blood supply
- Blood backup into R Heart
- Right heart strain
- Tachycardia
- V/Q Mismatch
- Often the only sign

**Circulation cut off to lung periphery**
- Sub pleural lung tissue ischemic /infarcted
- Irritated somatic sensory nerve endings
- Ischemic tissue inflamed and adheres to pleura
- Pleuritic Pain
- Pleural Friction Rub

www.thecalgaryguide.com
Complications of Pulmonary Embolism

Ischemic Lung
- Lung infarction
- Inflammatory process
  - ARDS

Obstructed Pulmonary Flow
- Failed oxygenate ventilate
  - High CO2
  - Resp failure

Increased PAP
- Acute R HF
  - Cardiogenic Shock
    - PEA
- Chronic
  - Pulmonary HTN
Role of Inflammation: Remember the GUT!

If gut is not balanced – there is a potential that gut bacteria is already in the lung and inflammation is in process
Management/Treatment of Pulmonary Embolus

**STABLE**

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Vasopressor</th>
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<tbody>
<tr>
<td>Heparins</td>
<td>Norepinephrine</td>
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</tbody>
</table>

- IV unfractionated
- Thrombolysis
  - Catheter directed thrombolysis
- SC LMWH
- SC Fondaparinux

**UNSTABLE**

- Fluids
- Anticoagulants
  - Heparins
- Vasopressor
  - Norepinephrine

**ORAL:**

- Factor IIa inhibitor: Dabigatran
- Factor Xa inhibitor: The BANS – Rivaroxaban, Apixaban

- VKA: Warfarin

**Surgical interventions**
Antidotes

**Direct Thrombin Inhibitors:** Idarucizumab

**Factor Xa Inhibitors:** Andexanet

**Vitamin K Antagonist:** Vitamin K

**Heparin:** Protamine Sulfate
Management of ACT for VTE: Guidelines 2019

Initial Anticoagulant Selection

Transition between AC

Resuming Anticoagulants After Bleeding

Excessive Anticoagulation and Bleeding Management

Invasive Procedure Management
Antiphospholipid Syndrome: Another Hypercoagulable State

- **Antiphospholipid antibodies** attack *phospholipid layer* or *proteins* that are bound to the endothelial cells and platelets.

- Platelet activation and aggregation

- Endothelial cell activation

- Pro-inflammatory cytokines

- **Coagulation** due to loss of anticoagulation activity

- T Cell activation

- Endothelial cell activation
Antiphospholipid Syndrome: Another Hypercoagulable State

Tissue factor (TF) pathway inhibitor

Anti thrombin III (AT III)

intrinsic heparin coating

THROMBIN

Cannot bind to Thrombomodulin

Thrombomodulin

Protein S

Protein C
Antiphospholipid Syndrome: Another Hypercoagulable State

Etiology: SLE, infection, medications, malignancy, chronic disease or idiopathic.

Thrombosis: Venous (DVT, PE), Arterial (Stroke, TIA) A/V microthrombosis (Nephropathy) microthrombosis, (skin ulcerations, Livedo Reticularis)

Pregnancy related complications: placental thrombus
Antiphospholipid Syndrome: Diagnostics and Treatment

Diagnostics: specific glycoproteins, SLE

Treatment:
- Without thrombotic syndrome: avoid risk factors, ASA for life
- With thrombotic syndrome: warfarin, LMWH during pregnancy.
Did you know that more than 12 million inpatients will receive heparin every year (in the US)?

With all that heparin being given...how many of you have taken care of a patient with heparin induced thrombocytopenia?
What signs and symptoms did you see in your HIT patient
Heparin Induced Thrombocytopenia

Type 1
Non Immune Disorder

Type 2*
Iatrogenic (Drug) Induced

HIT
HIT Type I

- Within 2 Days
- Direct Effect
- No Treatment Needed

HIT Type I
4-10 Days Post Heparin Dose

HIT II Antibodies Formed

Increased Thrombosis

Increased Stroke and Cardiac Arrest Risk

*Most common type of HIT diagnosed
*Type of HIT we are most worried about
Focus of our talk going forward
Pathophysiology of HIT

- **Heparin Given**
- IgG makes PF4 with heparin
- HIT antibodies develop
- PF4 changes due to heparin exposure to create a neoantigen
- HIT antibodies bind to PF4 neoantigen
- Platelets activated (HIT antibodies bind to PF4 on platelet surface)
- More PF4 is released and microvascular thrombosis occurs
- IgG coated platelets are removed by macrophages
- Platelets are destroyed/consumed
- **Thrombocytopenia**
What would make you wonder that a patient had HIT?
Ts of HIT

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>Thrombosis</th>
<th>Timing</th>
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</thead>
<tbody>
<tr>
<td>• Platelet count &lt; 150 or by &gt; 50%</td>
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<tr>
<td>• Most common manifestation</td>
<td></td>
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<tr>
<td>• DVT, PE, MI, TIA, stroke (ischemic), arterial thrombosis</td>
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<td></td>
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<tr>
<td>• Skin necrosis, end-organ failure, death</td>
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<tr>
<td>• Symptoms begin 4-10 days post heparin exposure</td>
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<tr>
<td>• Variants: rapid, refractory (delayed), and spontaneous</td>
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Bleeding

What about bleeding?
- Rare, if seen will be in unusual sites (GI bleed)
- Technically not a sign of HIT
Risk Factors

NOT related to:
- Age
- Dose
- Route

Women > Men ??

Differs according to TYPE of heparin
- Bovine > Porcine heparin

> incidence in post-surgical population
- Specifically cardiac and ortho

> incidence in unfractionated vs. low molecular weight
Problem with HIT

> 50% of patients will have a thromboembolic event

Mortality rate is ~ 20%

~10% of patients will suffer a major morbidity like amputation
What does the workup for HIT look like?
# Work Up

<table>
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<tr>
<th>Clinical</th>
<th>Laboratory</th>
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<tbody>
<tr>
<td>◦ 4Ts Score</td>
<td></td>
</tr>
<tr>
<td>◦ Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>◦ Thrombosis</td>
<td></td>
</tr>
<tr>
<td>◦ Timing</td>
<td></td>
</tr>
<tr>
<td>◦ Other cause for thrombocytopenia</td>
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4Ts Score

Taken from:
https://www.uptodate.com/contents/image?imageKey=HEME%2F116435&topicKey=HEME%2F90261&search=HIT&rank=1~150&source=see_link
Work Up

Clinical
- 4Ts Score
  - Thrombocytopenia
  - Thrombosis
  - Timing
  - Other cause for thrombocytopenia

Laboratory
- CBC
  - Platelets
  - Immunoassay
  - Functional assay
5 Phases of HIT

**Suspected HIT**
- Clinical picture suggestive of HIT
- Low platelet Levels (plt < 150,000 or fall of > 50%)
- Consider drawing assays

**Acute HIT**
- Functional assay and immunoassays confirm diagnosis
- Risk of thrombosis VERY HIGH at this time
- Lasts until platelet count normalizes

**Subacute A HIT**
- Platelet recovery has happened
- Both assays still **positive**

**Subacute B HIT**
- Platelet count **normal**
- Washed platelet functional assay **negative**
- Immunoassay **positive**

**Remote HIT**
- Platelet count **normal**
- Washed platelet functional assay **negative**
- Immunoassay now **negative**
Suspected HIT and Low 4Ts score

Intermediate 4Ts score

High 4Ts score

Keep heparin Running

Discontinue heparin

Start non-heparin anticoagulant (if appropriate)

Discontinue heparin

Initiate non-heparin anticoagulant

Immuoassay drawn but no results yet
Non HIT Event

- Immunoassay Negative
- Intermediate or High 4Ts score
  - Discontinue non-heparin anticoagulant
  - Restart heparin
Treatment Subacute B

Positive Immunoassay and

Intermediate or High 4Ts score

- Continue to avoid heparin
- Continue non-heparin anticoagulant
- Obtain functional assay
Treatment
Remote

Functional assay was positive but now negative and
Intermediate or High 4Ts score

HIT likely
Continue to avoid heparin
Continue non-heparin anticoagulant
Continue to follow platelets
Important Points

Vitamin K antagonists (e.g. Warfarin) should be avoided in patients with HIT until platelets recover

- Because they cause protein C deletion which can lead to venous limb gangrene
- After platelet recovery VKA should be initiated without a loading dose and overlapped with a parenteral anticoagulant for at least 5 days until INR has reached target
What are non heparin anticoagulants?

Parenteral:
- Argatroban, Bivalirudin, Danaparoid, Fondaparinux

Oral
- Dabigatran, Apixaban, Fivaroxaban, Edoxaban
Important point for discharge

Patients who develop HIT should wear a medical alert bracelet indicating they are allergic to heparin.

Current guidelines indicate that this bracelet should only be worn for 3 months as heparin use may be of benefit in the future.
Did you know....

Heparin was discovered 100 years ago (1919)!!
References


References


